domized to receive a vitamin K antagonist but excludes the 2,283 participants who were randomized to receive idraparinux. Because most of the bleeds in AMADEUS occurred in participants randomized to receive idraparinux, the authors should also provide c-statistics for major bleeding from these participants. For a valid comparison, could they also provide c-statistics for major bleeding from AMADEUS participants randomized to vitamin K antagonists, using each prediction score as a continuous variable but not including INR variability? This variable is not available until after the decision to initiate a vitamin K antagonist has already been made.

***Brian F. Gage, MD, MSc**
Martha J. Radford, MD

*Washington University School of Medicine
Campus Box 8005
660 South Euclid Avenue
St. Louis, Missouri 63110

http://dx.doi.org/10.1016/j.jacc.2012.09.053

Please note: Drs. Gage and Radford are originators of the $HEMORR_2HAGES$ risk-prediction score.

REFERENCE

1. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the $HEMORR_2HAGES$, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol 2012;60:861–7.

Reply

Dr. Singer and Drs. Gage and Radford dispute our use of "clinically relevant bleeding" as a safety endpoint, but this was the primary safety endpoint of the AMADEUS trial (1). Similarly, in the recent ROCKET AF trial, the primary safety endpoint was the composite of "major and clinically relevant non-major bleeding" (2). Our published analysis already included data on major bleeding while taking warfarin, but ultimately, clinically relevant bleeding would be highly relevant to patients and clinicians who wish to assess, in an informed manner (rather than by using guesswork), those who are at risk of important bleeding events in everyday clinical practice (3). Indeed, clinically relevant bleeding is indeed a sensible and medically meaningful endpoint, both for patients and physicians; in the AMADEUS trial, this robust endpoint was also centrally and blindly adjudicated.

Dr. Singer and Drs. Gage and Radford request the data from the idraparinux arm of the AMADEUS trial, and these have recently been published as a separate analysis (4). We did not feel that these data should be mixed with the warfarin data in our primary paper (1), given the significant differences between the 2 arms in the number of bleeding events. Furthermore, the development of idraparinux has ceased, and we made the pragmatic decision that clinicians would be more interested in the performance of these scores in warfarin-treated patients.

The analysis on intracranial bleeding is based on a small number of events, as is always the case in assessment of rare outcomes. Nevertheless, the retrieved area under the curve in receiver-operator characteristic curve analysis provided acceptable confidence intervals and a type I error probability of 3%.

The comments by Dr. Singer and Drs. Gage and Radford on the clinical use of the HAS-BLED score are misinformed. The "Labile INR" criterion (the L in HAS-BLED) only applies in a patient already taking wafarin. If the HAS-BLED score is being used to assess a nonanticoagulated patient's potential bleeding risk, then the labile INR criterion does not apply (and scores zero). In its original validation paper, the c-indexes for HAS-BLED in patients while taking vitamin K antagonists (VKA) (0.72), as well as those on antiplatelet agents alone or no antithrombotic therapy, were provided (c-indexes 0.91 and 0.85, respectively) (5). In addition, the labile INR criterion does not apply with the non-VKA anticoagulants, but our validation of the bleeding risk–prediction scores on idraparinux again clearly shows the value of HAS-BLED in non-VKA anticoagulation-treated patients (4).

However, risk assessment (whether for stroke or bleeding) is a dynamic process and should be repeated at regular intervals after the patient has begun antithrombotic therapy. This is when the labile INR criterion should be applied (especially because INR values should be available).

The HAS-BLED score has been shown to outperform the more complex $HEMORR_2HAGES$ and less practical ATRIA scores in other 'real-world' nontrial cohorts, even when major bleeding was the comparative endpoint (6,7). The limitations of the ATRIA score have also been highlighted previously (8). Furthermore, a high HAS-BLED score (≥3) is predictive of serious bleeding during bridging therapy, both in patients with atrial fibrillation and those without (9).

How should HAS-BLED be used? A high HAS-BLED score (≥3) is indicative of the need for regular review and follow-up but should not be used as a reason for withholding or stopping oral anticoagulation per se. The HAS-BLED score also makes clinicians think about the potentially correctable risk factors for bleeding; for example, uncontrolled blood pressure (the H in HAS-BLED), labile INRs if on warfarin (the L in HAS-BLED), and concomitant use of aspirin/NSAIDs or excessive alcohol use (the D in HAS-BLED). Finally, use of the HAS-BLED score has been advocated in various international guidelines and consensus documents [10–12].

Stavros Apostolakis, MD, PhD
Deirdre A. Lane, PhD
Yutao Guo, MD
Harry Buller, MD, PhD
***Gregory Y.H. Lip, MD**

*University of Birmingham Centre for Cardiovascular Sciences
City Hospital
Dudley Road
Birmingham B18 7QH
United Kingdom
E-mail: g.y.h.lip@bham.ac.uk

http://dx.doi.org/10.1016/j.jacc.2012.10.033

REFERENCES

1. Bousser MG, Bouthier J, Büller HR, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 2008;371:315–21.

2. Patel MR, Mahaffey KW, Garg J, et al., ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
3. Lip GY, Andreotti F, Fauchier L, et al; European Heart Rhythm Association. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a position document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. Thromb Haemost 2011;106:997–1011.
4. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR$_2$HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in non-warfarin anticoagulated atrial fibrillation patients, J Am Coll Cardiol 2013;61:386–7.
5. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. Chest 2010;138:1093–100.
6. Roldán V, Marín F, Fernández H, et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a 'real world' anticoagulated atrial fibrillation population. Chest 2012 Jun 21 [E-pub ahead of print].
7. Lip GY, Banerjee A, Lagrenade I, Lane DA, Taillandier S, Fauchier L. Assessing the risk of bleeding in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Circ Arrhythm Electrophysiol 2012;5:941–8.
8. Olesen JB, Pisters R, Roldans V, Marin F, Lane DA. The ATRIA risk scheme to predict warfarin-associated hemorrhage: not ready for clinical use. J Am Coll Cardiol 2012;59;194–5.
9. Omran H, Bauersachs R, Rübenacker S, Goss F, Hammerstingl C. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK Online bRiDging REgistRy (BORDER). Thromb Haemost 2012;108:65–7.
10. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association. Europace. 2012;14:1385–413.
11. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, Mitchell LB, Verma A, Nattel S; Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012;28:125–36.
12. Lip GY, Piotrponikowski P, Andreotti F, Anker SD, Filippatos G, Homma S, Morais J, Pullicino P, Rasmussen LH, Marín F, Lane DA. Thromboembolism and antithrombotic therapy for heart failure in sinus rhythm. An Executive Summary of a joint Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. Thromb Haemost. 2012;108:1009–22.

Straining With the Ventricular Assist Device and Right Ventricular Function

We read with great interest the paper by Grant et al. (1) in which they provide an analysis to support the use of strain imaging as a unique echocardiographic measure to predict right ventricular (RV) failure in patients undergoing left ventricular assist device (LVAD) placement. In their study, the value of RV strain was assessed using a multivariate logistic regression analysis and was found, not only to be significant in predicting RV failure, but also to provide incremental value to the Michigan RV risk score (2). The clinical relevance of such a prediction tool is not trivial because survival is significantly reduced in LVAD patients with ensuing RV failure.

The challenge for the practitioner is that the current VAD landscape is riddled with prognostic scores that hope to improve our clinical decision making at the time of patient evaluation for device candidacy. As the authors point out, no fewer than 8 strategies have been published specifically assessing the RV (2–9). This is in addition to at least 6 predictive risk scoring systems used to assess outcomes for pulsatile and continuous flow LVADs (10–15).

Strain measurements with echocardiography are derived principally from the deformation of the myocardial wall. Intuitively, patterns of RV strain should reflect loading conditions. It would have been revealing to determine the relationship between RV strain and right atrial pressure in their study population. Furthermore, the true clinical question may not be whether the patient will develop right ventricular failure, but instead, should a biventricular assist device be implanted. Including data on those patients who received a biventricular assist device would have provided even more valuable insights into the application of RV strain assessment in clinical practice.

The added value of RV strain to the many predictive indices for RV failure post-LVAD is promising, and as the authors suggest, will need to be further evaluated in a prospective multicenter manner. In the end, it may be that the quest for a precise RV prediction score is doomed to failure due to unanticipated events in the operating room. Significant bleeding requiring multiple blood transfusions, RV ischemia, and even accidental mechanical damage to the RV can contradict a clinical prediction model and render a patient with good RV function to one destined for RV failure after LVAD implantation.

Sunu S. Thomas, MD, MSc
Nir Uriel, MD
***Ulrich Jorde, MD**

*Division of Cardiology
Department of Medicine
College of Physicians & Surgeons
Columbia University Medical Center
Columbia University
630 West 168th Street
Box #93
New York, New York 10032
E-mail: upj1@columbia.edu

http://dx.doi.org/10.1016/j.jacc.2012.09.050

Please note: Dr. Uriel has received an honorarium from HeartWare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Grant AD, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. J Am Coll Cardiol 2012;60:521–8.
2. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score: a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163–72.
3. Drakos SG, Janicki L, Horne BD, et al. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. Am J Cardiol 2010;105:1030–5.